Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Rilpivirine (RPV, Edurant) (Last updated April 14, 2020; last reviewed April 14, 2020)

Formulations

Tablets: 25 mg

Fixed-Dose Combination Tablets:

- [Complera] Emtricitabine 200 mg/rilpivirine 25 mg/tenofovir disoproxil fumarate 300 mg
- [Juluca] Dolutegravir 50 mg/rilpivirine 25 mg
- [Odefsey] Emtricitabine 200 mg/rilpivirine 25 mg/tenofovir alafenamide 25 mg

When using fixed-dose combination (FDC) tablets, refer to other sections of the Drug Appendix for information about the individual components of the FDC. See also Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents.

For additional information, see Drugs@FDA or DailyMed.

Dosing Recommendations

Neonate and Infant Dose:

- Rilpivirine (RPV) is not approved for use in neonates or infants.

Children Aged <12 Years:

- RPV is not approved for use in children aged <12 years (for more information, see the Pharmacokinetics section below).

Child and Adolescent (Aged ≥12 Years and Weighing ≥35 kg) and Adult Dose:

- RPV 25 mg once daily with a meal in antiretroviral therapy (ART)-naive patients who have HIV RNA ≤100,000 copies/mL or in patients who are virologically suppressed (HIV RNA <50 copies/mL) with no history of virologic failure or resistance to RPV and other antiretroviral (ARV) drugs in the new regimen.

[Complera] Emtricitabine/Rilpivirine/Tenofovir Disoproxil Fumarate (TDF)

Child and Adolescent (Aged ≥12 Years and Weighing ≥35 kg) and Adult Dose:

- One tablet once daily with a meal in ART-naive patients with baseline viral loads ≤100,000 copies/mL. One tablet once daily can also be used to replace the current ARV regimen in patients who are currently on their first or second regimen and who have been virologically suppressed (HIV RNA <50 copies/mL) for at least 6 months with no history of treatment failure and no known mutations associated with resistance to the individual components of Complera.

Selected Adverse Events

- Depression
- Insomnia
- Headache
- Rash (can be severe and include drug reaction [or rash] with eosinophilia and systemic symptoms)
- Hepatotoxicity
- Altered adrenocorticotropic hormone stimulation test of uncertain clinical significance

Special Instructions

- **Do not start** RPV in patients with HIV RNA >100,000 copies/mL due to increased risk of virologic failure.
- Patients must be able to take RPV with a meal of at least 500 calories on a regular schedule (a protein drink alone does not constitute a meal).
- **Do not use** RPV with other non-nucleoside reverse transcriptase inhibitors.
- **Do not use** RPV with proton pump inhibitors (e.g., omeprazole, pantoprazole).
- Antacids should only be taken at least 2 hours before or at least 4 hours after RPV.
- H2 receptor antagonists (e.g., cimetidine, famotidine) should only be administered at least 12 hours before or at least 4 hours after RPV.
- Use RPV with caution when coadministering it with a drug that has a known risk of

[Juluca] Dolutegravir/Rilpivirine

Adult Dose:

- One tablet once daily with a meal as a complete regimen to replace the current ARV regimen in patients who have been virologically suppressed (HIV RNA <50 copies/mL) on a stable ARV regimen for at least 6 months with no history of treatment failure and no known mutations associated with resistance to the individual components of Juluca.
- Not approved for use in children or adolescents (see Simplification of Treatment section below).

[Odefsey] Emtricitabine/Rilpivirine/Tenofovir Alafenamide (TAF)

Child and Adolescent (Aged ≥12 Years and Weighing ≥35 kg) and Adult Dose:

- One tablet once daily with a meal in ART-naive patients with HIV RNA ≤100,000 copies/mL. One tablet once daily can also be used to replace a stable ARV regimen in patients who have been virologically suppressed (HIV RNA <50 copies/mL) for at least 6 months with no history of treatment failure and no known mutations associated with resistance to the individual components of Odefsey.

Torsades de Pointes (for more information, see CredibleMeds).

Metabolism/Elimination

- Cytochrome P450 (CYP) 3A substrate.

Rilpivirine Dosing in Patients with Hepatic Impairment:

- No dose adjustment is necessary in patients with mild or moderate hepatic impairment.
- RPV decreases tubular secretion of creatinine and slightly increases measured serum creatinine, but it does not affect glomerular filtration.

Rilpivirine Dosing in Patients with Renal Impairment:

- No dose adjustment is necessary in patients with mild or moderate renal impairment. However, RPV should be used with caution in patients with severe renal impairment or end-stage renal disease. These patients should be monitored more frequently for adverse events; renal dysfunction may alter drug absorption, distribution, and metabolism, leading to increased RPV concentrations.
- The FDC tablet Complera **should not** be used in patients with creatinine clearance (CrCl) <50 mL/min, and the FDC tablet Odefsey **should not** be used in patients with CrCl <30 mL/min.
- When using Complera, see the TDF section of the guidelines; when using Odefsey, see the TAF section.

Drug Interactions (see also the Adult and Adolescent Antiretroviral Guidelines and the HIV Drug Interaction Checker)

- *Metabolism:* Rilpivirine (RPV) is a cytochrome P450 (CYP) 3A substrate and requires dose adjustments when administered with CYP3A-modulating medications.
- A patient's medication profile should be carefully reviewed for potential drug interactions before RPV is administered.
- Coadministering RPV with drugs that increase gastric pH may decrease plasma concentrations of RPV.
- Antacids should only be taken at least 2 hours before or at least 4 hours after RPV.
- H2 receptor antagonists should only be administered at least 12 hours before or at least 4 hours after RPV.
- Do not use RPV with proton pump inhibitors.
- Rifampin and rifabutin significantly reduce RPV plasma concentrations; coadministration of rifampin and RPV is **contraindicated**. For patients who are concomitantly receiving rifabutin and RPV, the dose of RPV should be doubled to 50 mg once daily and taken with a meal.

- In a cohort of adolescent patients, RPV exposure was two to three times greater when RPV was administered in combination with darunavir/ritonavir (DRV/r) than when RPV was administered alone.[1]

Major Toxicities

- *More common:* Insomnia, headache, rash.
- *Less common (more severe):* Depression or mood changes, suicidal ideation.
- In studies of adults, 7.3% of patients who were treated with RPV showed a change in adrenal function characterized by an abnormal 250-microgram adrenocorticotropic hormone (ACTH) stimulation test (peak cortisol level <18.1 micrograms/dL). In a study of adolescents, six out of 30 patients (20%) developed this abnormality.[2] The clinical significance of these results is unknown.

Resistance

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation.

Transmitted drug resistance to second-generation non-nucleoside reverse transcriptase inhibitors (NNRTIs) may be present in infants and children who have recently received a diagnosis of HIV.

Pediatric Use

Approval

With the viral load and antiretroviral (ARV) resistance restrictions noted above, RPV used in combination with other ARV agents,[2] the fixed-dose combination (FDC) tablet emtricitabine/rilpivirine/tenofovir disoproxil fumarate (FTC/RPV/TDF; Complera),[3] and the FDC tablet emtricitabine/rilpivirine/tenofovir alafenamide (FTC/RPV/TAF; Odefsey) are all approved by the Food and Drug Administration (FDA) for use in persons aged ≥12 years and weighing ≥35 kg.[4] The FDC tablet dolutegravir/rilpivirine (DTG/RPV; Juluca) is not approved for use in pediatric or adolescent patients at the time of this review.[5]

Efficacy in Clinical Trials

An RPV-containing regimen has been compared to an efavirenz (EFV)-containing regimen in two large clinical trials in adults, ECHO and THRIVE. In both studies, RPV was shown to be noninferior to EFV. Patients with pretreatment HIV viral loads ≥100,000 copies/mL who received RPV had higher rates of virologic failure than those who received EFV. These findings resulted in FDA approval for initial therapy with RPV only in patients with HIV viral loads ≤100,000 copies/mL.[6-9]

A study of ART-naive adolescents aged 12 to 18 years demonstrated that RPV 25 mg, given once daily in combination with two nucleoside reverse transcriptase inhibitors (NRTIs), was well tolerated over 48 weeks. Among adolescents with baseline viral loads ≤100,000 copies/mL, 86% had a virologic response at 24 weeks and 79% had a virologic response at 48 weeks. Among adolescents with baseline viral loads >100,000 copies/mL, 38% had a virologic response at 24 weeks and 50% had a virologic response at 48 weeks.[10]

Patients must be able to take RPV on a regular schedule and with a full meal, which may limit its usefulness for some adolescents with irregular schedules. The FDC formulation Odefsey is a small pill and can be useful for certain patients who have difficulty swallowing pills but want to switch from a multipill regimen and who do not have any drug resistance mutations that are associated with the components of Odefsey.

A Spanish multicenter observational study enrolled 17 adolescents (aged <18 years) who acquired HIV perinatally to receive FTC/RPV/TDF (Complera) as part of an off-label medication use program. At the time of enrollment, 12 patients were on a protease inhibitor-based regimen, four were on an NNRTI-based regimen, and one had not received antiretroviral therapy (ART). After a median follow-up of 90 weeks (for participants with undetectable viral loads at baseline) or 40 weeks (for participants with detectable viral loads at baseline), 86% and 89% of patients, respectively, achieved and maintained an undetectable viral

load. None of the patients discontinued RPV-based therapy because of adverse events (AEs); no skin rashes or central nervous system (CNS)-related events were observed. In addition, serum lipids improved and two adolescents with a history of insomnia and abnormal dreams while receiving EFV-based therapy did not report similar problems while receiving RPV-based therapy.[11]

Pharmacokinetics

The pharmacokinetics (PKs), safety, and efficacy of RPV in children aged <12 years have not been established but are currently being studied in patients aged 6 years to <12 years and weighing ≥17 kg (*ClinicalTrials.gov* identifier NCT00799864). The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) has agreed that the use of RPV may be appropriate in certain children aged <12 years and weighing ≥35 kg. However, the Panel advises consulting an expert in pediatric HIV infection prior to prescribing RPV in a child in this age and weight group.

An international (India, Thailand, Uganda, and South Africa) Phase 2 trial, PAINT TMC278, investigated a 25-mg dose of RPV given in combination with two NRTIs in ARV-naive adolescents aged 12 years to <18 years who weighed ≥32 kg and who had viral loads ≤100,000 copies/mL.[10] In the dose-finding phase of the study, 11 youth aged >12 years to ≤15 years and 12 youth aged >15 years to ≤18 years underwent intensive PK assessment after they took an observed dose of RPV with a meal. PKs were comparable to those in adults; results are listed in the table below.[12]

Table A. Rilpivirine Pharmacokinetics in Adults and Adolescents Aged 12 Years to <18 Years

Parameter	Adults	Adolescents Aged 12 Years to <18 Years
Dose	RPV 25 mg once daily	RPV 25 mg once daily
Number of Participants Studied	679	34
AUC_{24h} (ng•h/mL)		
Mean ± SD	2,235 ± 851	2,424 ± 1,024
Median (Range)	2,096 (198–7,307)	2,269 (417–5,166)
C_{0h} (ng/mL)		
Mean ± SD	79 ± 35	85 ± 40
Median (Range)	73 (2–288)	79 (7–202)

Source: Adapted from Rilpivirine [package insert]. Food and Drug Administration. 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/202022s011lbl.pdf.[2]

Key: AUC_{24h} = area under the curve after 24 hours; C_{0h} = plasma concentration just prior to next dose; RPV = rilpivirine; SD = standard deviation

In a PK study of youth aged 13 to 23 years who received RPV,[1] RPV exposure was comparable to the exposure observed during the PAINT study in patients who received 25-mg doses of RPV without DRV/r and substantially higher than the exposure observed in those who received 25-mg doses of RPV with DRV/r (RPV area under the curve in this study was 6,740 ng·h/mL). No dose adjustments are currently recommended for adults when RPV is coadministered with DRV/r , where a similar two-fold to three-fold increase in RPV exposure has been reported.[2]

RPV has been reported to have fewer CNS AEs than EFV, and it has been promoted as a replacement ARV drug for some patients who experience CNS effects while receiving EFV. However, there has been concern that the prolonged half-life of EFV might result in residual drug levels that could have an impact on RPV levels. A Thai study evaluated 20 Thai adolescents 4 weeks after they switched from EFV to RPV. The PK parameters of RPV in this study population were comparable to those in previous pediatric (PAINT) and adult (ECHO/THRIVE) PK substudies. No virologic failure was detected at 12 or 24 weeks and no patients

discontinued RPV because of AEs.[13]

Simplification of Treatment

Juluca is an FDC tablet that contains DTG 50 mg and RPV 25 mg. The results from two trials in adults (SWORD-1 and SWORD-2) supported FDA approval of DTG/RPV as a complete regimen for treatment simplification or maintenance therapy in certain patients. The two identical SWORD trials enrolled 1,024 patients with suppressed viral replication who had been on stable ART for at least 6 months and had no history of treatment failure or evidence of resistance mutations that are associated with DTG or RPV. The participants were randomized to receive DTG/RPV or to continue their suppressive ARV regimen. After 48 weeks of treatment, 95% of patients in both arms maintained HIV RNA <50 copies/mL.[14] After 52 weeks, the participants who had been randomized to continue their suppressive ARV regimen were switched to DTG/RPV. At 100 weeks of treatment, 86% of the early switch patients and 93% of the late switch patients remained virologically suppressed.[15] More AEs were reported and more AEs led to discontinuation in the DTG/RPV arm during the comparative randomized phase. In a subgroup of SWORD study patients whose original ARV regimen contained TDF, small but statistically significant increases in hip and spine bone mineral density were observed.[16] Although DTG/RPV as Juluca is not approved for use in adolescents, the doses of both component drugs that make up Juluca are approved for use in adolescents. This product may be appropriate for certain adolescents; however, because the strategy of treatment simplification has not been evaluated in adolescents, who may have difficulties adhering to therapy, the Panel **does not recommend** using Juluca in adolescents and children until more data are available.

Long-Acting, Injectable Rilpivirine

A long-acting, injectable formulation of RPV is under development as a treatment for adult patients; this formulation is designed to be administered concurrently with a cabotegravir long-acting injectable.[17-19] IMPAACT study 2017, More Options for Children and Adolescents (MOCHA), is currently enrolling participants to evaluate the safety, tolerability, acceptability, and PKs of this injectable regimen in adolescents.

Toxicity

In the PAINT study, the observed AEs were similar to those reported in adults (e.g., somnolence, nausea, vomiting, abdominal pain, dizziness, headache). The incidence of depressive disorders was 19.4% (seven of 36 participants) compared to 9% in the Phase 3 trials in adults. The incidence of Grade 3 and 4 depressive disorders was 5.6% (two of 36 participants).[2]

Six out of 30 adolescents (20%) with a normal ACTH stimulation test at baseline developed an abnormal test during the trial. There were no serious AEs, deaths, or treatment discontinuations that were attributed to adrenal insufficiency. The clinical significance of abnormal ACTH stimulation tests is not known, but this finding warrants further evaluation.[2]

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